

REMARKS

The Office Action

Claims 30-47, 50-51, and 53-78 are pending in this application, but claims 32, 35, 38-42, and 45 are withdrawn from consideration. Claims 30-31, 33-34, 36-37, 43-44, 46-47, 50-51, 53-55, 57, 59, 61, and 72-74 stand rejected under 35 U.S.C. § 112, first paragraph for inadequate written description. All examined claims stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. Claims 30-31, 33-34, 36-37, 43-44, 46-47, 53-55, 57, 59, 61, and 72-74 stand rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. Each of these rejections are address individually below.

Rejections Under 35 U.S.C. § 112, first paragraph

Written Description

Claims 30-31, 33-34, 36-37, 43-44, 46-47, 50-51, 53-55, 57, 59, 61, and 72-74 stand rejected under 35 U.S.C. § 112, first paragraph for inadequate written description. Thus, claims 56, 58, 60, 62-71, and 75-78 are not rejected on this basis. Specifically, the Examiner asserts that the specification fails to describe the claimed invention in a manner that conveys with reasonable clarity to those skilled in the art that Applicants were in possession of that invention.

In response, Applicants have amended claim 30, the sole independent claim, to be commensurate in scope with claim 63 which was not rejected for inadequate written description. Specifically, claim 30 now encompasses the use of nucleic acids encoding polypeptides having fewer than 299 amino acids, wherein at least 150 amino acids are at least 90% identical to the corresponding region of amino acid residues 1-185 of SEQ ID NO:2. Necessarily, claims 63 and 75 have been canceled and claim 64 has been amended to depend from claim 30.

Applicants have overcome this rejection by amendment and the rejection should now be withdrawn.

Enablement

All pending claims stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement. The Examiner asserts that, while being enabling for a method of lowering cholesterol by intravascular administration of the identified recombinant adenovirus to a mammal lacking a normally functioning ApoE gene, the specification does not enable

a method of lowering cholesterol in any mammal without inducing hypertriglyceridemia by administering via any route of delivery or expressing in any tissues in said mammal any nucleic acid molecule, including a recombinant adenovirus containing a nucleic acid encoding a polypeptide having fewer than 299 amino acids, wherein said polypeptide comprises a region of at least 150 amino acids having at least 80% sequence identity to a mature, native, human apoE3 polypeptide.

Office Action mailed April 21, 2004; page 7 (emphasis removed).

The rejection is based on (i) the overbreadth of the claims, (ii) the state and unpredictability of the art, and (iii) the amount of direction or guidance provided by the specification. Each of these bases of rejection is addressed individually below.

Claim Breadth

The Examiner asserts that many limitations of the claims are overly broad and are not commensurate with the scope of enablement provided. Specifically, the Examiner asserts that the claims are overly broad with respect to “a polypeptide having fewer than 299 amino acids as long as it comprises a region of at least 150 amino acids having at least 80% sequence identity to any mature, native, human apoE polypeptide” and “any route of administering any nucleic acid molecule.”

The present claim amendments specifically address and overcome this basis of rejection. Claim 30, as presently amended, requires that the nucleic acid encoding the truncated apoE protein be contained within a vector. Additionally, the polypeptides encoded by the vectors of the claimed method are now required to be 90% identical to

amino acids 1-185 of SEQ ID NO:2. Finally, the route of administration is limited to intravascular administration (e.g., intravenous and intra-arterial injection). Thus, the amended claims are clearly within the scope of the enablement provided in the specification.

General Unpredictability of the Art

The Examiner asserts that, as of the effective filing date of the application, “the state of the gene therapy art remains unpredictable particularly for the attainment of the desired prophylactic and/or therapeutic effects” (*Office Action*, page 9). In support of unpredictability, the Examiner cites numerous prior art publications as evidence that gene therapy historically has been unpredictable.

Applicants strenuously disagree with this basis of rejection and strongly assert that it is Applicants’ work that removes the unpredictability in the use of vectors encoding apoE polypeptide fragments for lowering plasma cholesterol without increasing hypertriglyceridemia.

With respect to the Examiner’s characterization of the unpredictability of the art, the Examiner has either mischaracterized the art or refused to consider the art in conjunction with Applicants’ teachings.

The Examiner mischaracterized Dang *et al.* and misapplies the teachings to the present invention. The Examiner, quoting on Dang *et al.*, asserts:

[a]lthough significant progress has been achieved in our understanding of the limitation of gene therapy by suboptimal vectors, host immunological responses to the vectors, and the lack of long term stable expression, the major challenge that limits clinical translation remains in achieving efficient gene delivery to target tissues.

Office Action, sentence bridging pages 9 and 10. Emphasis original.

This particular teaching of Dang *et al.* is irrelevant to the instant invention. In the

sentence immediately preceding the one quoted by the Examiner, Dang *et al.* make clear that their conclusions relate specifically to “the future of cancer gene therapeutics.”

Applicants’ invention is not a cancer treatment, but rather one that lowers plasma cholesterol. As such, Applicants’ method does not require specific delivery and gene expression by any one particular target tissue, as is the case for potential gene therapies for cancer in which the therapeutic protein is desirably expressed by one particular cell type (e.g., the tumor or immune cells). Applicants do not claim a method that requires tissue-specific expression. The fact that intravenous injection of a vector capable of expressing the apoE polypeptide fragments is highly expressed in the liver—an important endogenous source of native apoE—is a desirable, but merely incidental, consequence of Applicants’ method.

The Examiner’s reliance on Romano *et al.* is misplaced. The Examiner points out that Romano *et al.* state that “the effectiveness of gene therapy programs is still questioned” and that

further improvements of gene transfer technology, especially for *in vivo* gene delivery applications, regulation and control of the transgene expression post-cell transduction, and a variety of complex safety matters.

As Applicants discussed previously, these teachings by Romano *et al.* do not demonstrate that gene therapy does not work. They merely demonstrate the some optimization is necessary. The required optimization requires nothing more than routine experimentation. Romano *et al.* further note that “more than 300 Phase I and phase II gene-based clinical trials have been conducted worldwide for the treatment of cancer and monogenic disorders” and that “[t]here are 27 currently active gene therapy protocols for the treatment of HIV-1 infection in the USA” (abstract). The approval for such a large number (> 300) of gene therapy trials by the worldwide regulatory authorities is evidence not that gene therapy does not work, but rather that gene therapy works but needs to be optimized for each individual disease indication and therapeutic regimen. Thus, the

Examiner's reliance on Romano *et al.* to evidence a lack of enablement is not well founded.

In another attempt to demonstrate the unpredictability of the gene therapy art, the Examiner relies on Kawashiri *et al.* who state that "somatic gene therapy is a viable approach to the therapy of several lipid disorders for which therapies are currently inadequate" and "the next decade is therefore likely to witness several clinical trials of gene therapy for lipid disorders." (Office Action, page 10, quoting Kawashiri *et al.*). First, even accepting *arguendo* that Kawashiri's conclusion is correct—that viable gene therapy approaches for lipid disorders are inadequate—Kawashiri arrived at this conclusion in 2000. Kawashiri did not have the benefit of reviewing Applicants' method which was not published in the scientific literature until 2001 (Kypreos *et al.*, *FASEB J.* 15: 1598-1600, 2001; *Biochemistry* 40: 6027-6035, 2001). Thus, the Examiner's reliance here is also misfounded.

Second, by relying on this specific passage, the Examiner appears to require that a successful clinical trial be conducted in order to satisfy the enablement requirement. This is not the law. Human testing is not required, for enablement purposes, to support claims of an *in vivo* utility. The Federal Circuit has repeatedly stated that:

Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings ... Congress has given the responsibility to the FDA, not to the [PTO], to determine ... whether drugs are sufficiently safe.

Scott v. Finney, 34 F.3d 1058,1063 (Fed. Cir. 1994), affirming *In re Watson*, 517 F.2d 465, 476 (C.C.P.A. 1975) and *In re Sichert*, 566 F.2d 1154, 1160 (C.C.P.A. 1977).

Furthermore, the Federal Circuit, in reversing a Board of Patent Appeals and Interferences decision that *in vitro* data did not support *in vivo* applications, stated:

the stage at which an invention in this field becomes useful is well before it is ready to be administered to humans.

In re Brana, 51 F.3d 1560, 1568 (Fed. Cir. 1995).

The law is very clear on the interpretation of the enablement requirement. The first paragraph of § 112 “requires nothing more than objective enablement” and, in a case in which the Patent Office questions the enablement of a claim (*In re Marzocchi*, 439 F.2d 220 (C.C.P.A. 1971)), evidence from sources other than human efficacy trials is acceptable.

Applicants provide much more than the *in vitro* data of *Brana* which was sufficient to enable an *in vivo* use. Applicants provide actual *in vivo* testing in an accepted animal model of the relevant disease condition.

Next, the Examiner points to the results of Tsukamoto *et al.* (*J. Clin. Invest.* 100: 107-114) and Kashyap *et al.* (*J. Clin. Invest.* 96: 1612-1620, 1995) to demonstrate that:

at the effective filing date of the present application it was apparent that the biological activity of the ApoE proteins with respect to their ability to maintain cholesterol and triglyceride homeostasis *in vivo*, at least in ApoE-deficient mice, is unpredicable.

Office Action at page 11.

Applicants respectfully submit that the Examiner’s application of Tsukamoto *et al.* and Kashyap *et al.* is irrelevant on the question of enablement. Specifically, whether or not overexpression of any of the native apoE proteins results in hypertriglyceridemia provides no insight into whether expression of a vector encoding an apoE fragment is capable of reducing plasma cholesterol without inducing hypertriglyceridemia because there the cleavage of the C-terminus is designed to prevent the hypertriglyceridemic effect.

Furthermore, these reference support rather than refute Applicants’ contention that the presently claimed invention is fully enabled by the specification. Kashyap *et al.*, published in 1995, and Tsukamoto *et al.*, published in 1997, demonstrates that gene

therapy methods similar to that of the present invention, but using a full length apoE protein, are capable of imparting a therapeutic effect by lowering plasma cholesterol in a relevant animal model.

The Examiner's reliance on Yoshida *et al.* (*Circulation* 104: 2820-2825, 2001) to demonstrate the unpredictability in the use of apoE proteins is also misplaced. The Examiner characterized the Yoshida method as transplanting apoE^{-/-} bone marrow cells that express a human apoE protein into apoE-deficient mice. The Yoshida method differs from Applicants in at least two critical ways. First, Yoshida *et al.*, like Kashyap *et al.* and Tsukamoto *et al.*, use a full length apoE protein rather than a fragment. Second, Yoshida *et al.* perform a bone marrow transplantation. This is a significantly different procedure than the intravascular administration of an expression vector, as is required in the instant claims.

Finally, the Examiner attempts to rely on Applicants' own post-filing publication to evidence non-enablement. Specifically, the Examiner relies on the statement in Kypreos *et al.*, *J. Biol. Chem.* 276: 19778-19786, 2001) which reads (Examiner's emphasis):

The identification of amino acid residues within the carboxy terminal region of apoE, which mediate the hypertriglyceridemic effect of apoE is the subject of ongoing research.

Here again, the Examiner's reliance is misplaced. The present invention encompasses apoE fragments having a C-terminal truncation sufficient to ablate the hypertriglyceridemic effect of the full protein. There is no need to identify the specific amino acids responsible for that effect because, to fall within the claims, those amino acids are necessarily deleted. Furthermore, the existence of ongoing research cannot negative patentability. Alexander Graham Bell, for example, obtained a patent on the telephone in the 1880's. Since then, billions of dollars have been spent on research and hundreds of patents have issued on telephony improvements. Clearly, the presence of

ongoing research alone is insufficient to negate patentability.

In sum, the references cited by the Examiner do not demonstrate that there is unpredictability in the art with respect to the use of gene therapy for delivering apoE fragments to lower plasma cholesterol without inducing hypertriglyceridemia. To the contrary, several of the references (e.g., Kashyap *et al.* and Tsukamoto *et al.*) demonstrate that gene therapy techniques, when used to express a full-length apoE protein, can have a measurable therapeutic effect in a relevant animal model of hypercholesterolemia.

The Amount of Direction or Guidance Presented

The Examiner asserts that

the instant specification fails to provide sufficient guidance for a skilled artisan on how to lower the total serum cholesterol level without inducing hypertriglyceridemia in any mammal using [a protein of the invention].

Office Action, page 12 (emphasis original).

In support of this basis of rejection, the Examiner relies on the Kawashiri *et al.* to demonstrate that the “apoE knockout mouse is not a representative mouse model for any lipid disorder;” Orkin *et al.*, to demonstrate that “mouse models often do not faithfully mimic the relevant human conditions [citation omitted], and that animal models are not satisfactory for studying many important disorders, including cystic fibrosis, various cancers, and AIDS;” Dijk *et al.* and Linton *et al.* to demonstrate that “in LDL receptor-deficient mice... apoE3 via adenovirus-mediated gene transfer did not result in a reduction of hypercholesterolemia, and severe hypertriglyceridemia was always induced;” and Yoshida *et al.* to demonstrate that “apoE-deficient mice receiving apoE^{-/-} bone marrow cells that express human apoE3 or apoE2 or apoEcys142 have cholesterol levels increasing with age and the cholesterol levels are not affected by apoE expression.” Applicants respectfully submit that, for the reasons discussed below, none of these

references demonstrate that the instant specification fails to enable the invention as presently claimed.

The Examiner mischaracterizes the teachings of Kawashiri *et al.* Nowhere does Kawashiri *et al.* suggest that the usefulness of the apoE^{-/-} mouse model is limited to the rare genetic disorders identified by the Examiner. In the section to which the Examiner refers, Kawashiri *et al.* merely note that there are genetic disorders (e.g., familial dysbetalipoproteinemia) that result in defective apoE proteins and these disorders may be candidates for treatment using gene therapy. Applicants can find no teaching which disparages the use of apoE^{-/-} mice as a model for other lipid disorders.

The Examiner's reliance on the findings of Orkin *et al.* is also misplaced as it relates to the instant invention. Orkin *et al.* finds that:

5. There is a clear and legitimate need for clinical studies to evaluate various aspects of gene therapy approaches... Indeed, in some cases, such as cystic fibrosis, cancer, and AIDS, animal models do not satisfactorily mimic the major manifestations of the corresponding human disease.

Orkin *et al.*, Executive Summary, paragraph bridging pages 1 and 2 (emphasis added).

Orkin *et al.* does not find that all animal models are unsatisfactory; merely the ones then considered for cystic fibrosis, cancer, and AIDS. The instant invention relies on an animal model of hypercholesterolemia; a model for a disease not considered by Orkin *et al.* As such, the Examiner is applying the findings of Orkin *et al.* far more broadly than is warranted.

The teachings of Dijk *et al.* and Linton *et al.* are not inconsistent with Applicants' data and the Examiner's reliance on them to prove non-enablement is misplaced. The Examiner points out that these references demonstrate that overexpression of apoE in a lipoprotein receptor-deficient (LDLR^{-/-}) mouse does not correct the hypercholesterolemia. These teachings are predictable but irrelevant on the question of enablement of the

instant invention. It is well known that the LDLR is a downstream apoE receptor.¹ Thus, one would not expect overexpression of the upstream receptor ligand, apoE, to impart a therapeutic benefit because the absence of the major species of apoE receptor breaks the downstream signal transduction mechanism. Furthermore, the fact that apoE overexpression fails to correct hypercholesterolemia in an LDLR^{-/-} is irrelevant to the question of whether the apoE^{-/-} model used by Applicants enables the claimed invention because Applicants' model is not LDLR-deficient.

Finally, the Examiner points to the teachings of Yoshida *et al.* to demonstrate that the prior art is unpredictable and to evidence that the instant specification provides insufficient guidance. The Examiner points out that, in Yoshida *et al.*, apoE-deficient mice receiving apoE^{-/-} bone marrow cells that express a human apoE have cholesterol levels that increase with age. Applicants first point out that the method used by Yoshida *et al.* to overexpress an apoE protein—by transplantation of bone marrow cells expressing a heterologous protein—is completely unrelated to Applicants' method with intravascularly injects a vector expressing a homologous apoE protein fragment. Second, the basic finding that expression of an apoE protein increases, rather than decreases, plasma cholesterol is contrary to the vast majority of the scientific evidence (see, for example, Dijk *et al.*). Furthermore, Linton *et al.*, a reference previously relied upon by the Examiner, demonstrated that reconstitution of apoE^{-/-} mice with apoE^{+/+} bone marrow reduced hypercholesterolemia. Thus, it is most likely that the lack of therapeutic effect reported by Yoshida *et al.* was merely a defect in experimental design which, once optimized, would yield the opposite result.

In view of the foregoing, Applicants respectfully submit that the present specification, in combination with the prior art, is sufficient to allow a skilled artisan to

¹ See, for example, Dijk *et al.* at page 336, right column: "One important receptor involved in remnant lipoprotein uptake is the LDL receptor, an apoB/E specific receptor which can be responsible for up to 75% of total remnant uptake."

practice the claimed invention using no more than routine experimentation. Applicants request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, second paragraph

Claims 30-31, 33-34, 36-37, 43-44, 46-47, 53-55, 57, 59, 61, and 72-74 stand rejected under 35 U.S.C. § 112, second paragraph for indefiniteness. Specifically, the Examiner asserts that, in claim 30, the phrase “having at least 80% sequence identity to the corresponding region of a mature, native, human apoE polypeptide” is unclear.

Applicants disagree. However, in order to expedite prosecution, the phrase has been replaced with “having at least 90% sequence identity to the corresponding region of amino acid residues 1-185 of SEQ ID NO:2.” Applicants submit that the claim, as amended, is not indefinite and this rejection should be withdrawn.

The Examiner further rejects claim 73 for incompleteness. Claim 73 is canceled herewith. This rejection should be withdrawn.

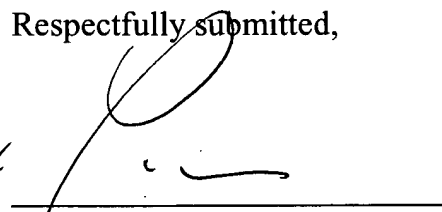
CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is requested. Enclosed is a petition to extend the period for replying for three months, to and including October 21, 2004. If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date

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